(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 2003/101386 A3

(51) International Patent Classification[7]: C07H 21/02, 21/04, C12N 5/00, 15/00, 15/63, A01N 63/00

(21) International Application Number: PCT/US2003/016961

(22) International Filing Date: 29 May 2003 (29.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/384,228	30 May 2002 (30.05.2002)	US
60/460,023	3 April 2003 (03.04.2003)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 7 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: KINASE SUPPRESSOR OF RAS INACTIVATION FOR THERAPY OF RAS MEDIATED TUMORIGENESIS

(57) Abstract: The present invention relates to methods and compositions for the specific inhibition of kinase suppressor of Ras (KSR). In particular, the invention provides genetic approaches and nucleic acids for the specific inhibition of KSR, particularly of KSR expression. The invention relates to antisense oligonucleotides and the expression of nucleic acid which is substantially complementary to KSR RNA. Oligonucleotide and nucleic acid compositions are provided. The invention provides methods to inhibit KSR, including inhibition of KSR expression. Methods for blocking gf Ras mediated tumorigenesis, metastasis, and for cancer therapy are provided.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/16961

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07H 21/02, 21/04; C12N 5/00, 15/00, 15/63; A01N 63/00
US CL : 536/23.1, 24.5; 435/320.1, 325, 455; 424/93.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.1, 24.5; 435/320.1, 325, 455; 424/93.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN, WEST, MEDLINE, CAPLUS, BIOSIS, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/21820 (THE REAGENTS OF THE UNIVERSITY OF CALIFORNIA) 19 June 1997 (19.06.1997), abstract, page 4.	1-8
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Y		9-16
Y	ROJANASAKUL, Y., Antisense Oligonucleotide Therapeutics: Drug Delivery and Targeting, Advanced Drug Delivery Reviews, 1996, Vol. 18, p. 115-131, especially, abstrct, page 119, 120.	9-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
17 June 2004 (17.06.2004)

Date of mailing of the international search report
17 AUG 2004

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Int tional application No.
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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-16

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/16961

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-16, drawn to an oligonucleotide that is substantially complementary ro a region of KSR RNA, such as any one of SEQ ID Nos. 1 and 3-8, and said oligomucleotide inhibits the expression of KSR, a recombinant DNA molecule comprising a nucleic acid encoding an antisense RNA complementary to mammalian KSR RNA or a portion thereof, and an expression vector comprising said nucleic acid.

Group II, claim(s) 17-28, drawn to a pharmaceutical composition comprising a therapeutically amount of an antisense oligonucleotide of claim 1, a method of inihibiting expression of mammalian KSR, and a method of treating or preventing a hyperproliferative condition associated with the expression of gf-Ras by using a compound or an agent, such as an antisense oligonucleotide that inhibits the expression of mammalian KSR.

Group III, claim(s) 29, drawn to a method of identifying compounds or agents which inhibit the expression of KSR.

Group IV, claim(s) 30, drawn to a ribozyme that cleaves KSR mRNA.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature that is shared by groups I-III is the antisense oligonucleotide which is complementary to a region of KSR RNA. Group IV reads on a ribozyme that cleaves KSR RNA. WO 97/21820 discloses nucleic acid sequence encoding the kinase suppressor of Ras (ksr), which has nucleotide sequence that is 100% identical to SEQ ID Nos. 1 and 4-6 (see computer printouts). WO 97/21820 also teaches a method for screening chemical libraries for lead compounds for a pharmaceutical agent useful in the diagnosis or treatment of disease associated with ksr activity or ksr-dependent signal transduction, and using antisense nucleic acids or ribozymes comprising the ksr sequences or their complements or reverse complements in gene therapy applications (e.g. abstract, page 4, first paragraph). Thus, there is no special technical feature that is contributed over the prior art by the present invention. Therefore, groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1.